Amendments to the Specification

Please replace paragraph [0022] with the following amended paragraph:

[0022] Nuclear proteins are imported into the nucleus through aqueous channels that span the nuclear envelope called nuclear pore complexes (NPCs). Although ions and molecules less than ~20-40 Da can diffuse passively through the nuclear pore complexes, larger proteins are transported by saturable pathways that are energy- and signal-dependent. The signals that specify ~~nuclear protein import (NLSs)~~ nuclear protein import (NLSs) are commonly short stretches of amino acids rich in basic amino acid residues, although other classes of NLSs have been described recently. The initial step in the import of proteins containing basic amino acid-type NLSs occurs in the cytosol, where the NLS-containing proteins are bound to a receptor (variously called the NLS receptor, importin α, and karyopherin (13). The substrate-receptor complex then associates with the cytoplasmic face of the nuclear pore complexes, and with the participation of other cytosolic factors, is transported through a gated channel in the nuclear pore complexes to the nuclear interior. The in vivo events of NLS-mediated nuclear import can be duplicated in an in vitro system using digitonin-permeabilized cells supplemented with cytosolic extracts and ATP (14). Transport in this in vitro assay is blocked by the same inhibitors that block in vivo import, is rapid, and is easily quantified.

Please replace paragraph [0024] with the following amended paragraph:

[0024] Although FGF-1 ~~contains an NTS~~ contains a nuclear translocation signal (NTS), nuclear translocation requires an exogenous and not an endogenous pathway. The NTS of FGF-1, NYKKPKL, is able to direct the expression of the bacterial β-galactosidase (βgal) gene to the nucleus of transfected NIH 3T3 cells, but this NTS is unable to target either FGF-1 itself of a FGF-1-βgal fusion protein into the nucleus, suggesting that FGF-1 may contain an additional sequence which prevents endogenously expressed FGF-1 from being translocated into the nucleus. Zhan, X., et al., Biochem. Biophys. Res. Commun. (1992), 188(3), 982-91.

Please replace paragraph [0029] with the following amended paragraph:

[0029] In all cells, the lipid bilayer of cell membranes serves as a selective barrier for the passage of charged molecules, with the internalization of hydrophilic macromolecules being achieved through classical transport pathways (Hawiger, J., Curr Opin Chem Biol. 3, 89-94 (1999), Schwartze, S. R., et al., Trends in Cell Biology 10, 290-295 (2000)). These classical mechanisms of internalization involve receptor-mediated endocytosis or transporter dependent uptake (Cleves, A. E., Current Biology 7, R318-R320 (1997)). In contrast, an increasing number of molecules have been discovered that lack classical import and/or export signals (Cleves, A. E., Current Biology 7, R318-R320 (1997)). These molecules gain direct access to either cytoplasmic or nuclear compartments using unconventional processes of which the mechanisms remain largely unknown. These novel mechanisms are generally termed "nonclassical" and refer to transport pathways being used that are atypical. Relevant examples of this latter type are found in the gene-encoded proteins of HIV-1 TAT (Frankel, A. D. and Pabo, C. O. Cell 55,1189-1193 (1988)), herpes virus VP22 (Elliott, G. and O'Hare, P. Cell 88, 223-233 (1997)), and Antennapedia, Antp (Derossi, D., et al., J. Biol. Chem. 269,10444-10450 (1994)). It is now well established that the full-length proteins of HIV-1 TAT (Helland D. E., et al., J Virol 65, 4547-4549 (1991)), and VP22 (Pomeranz L. E. and Blaho J. A., J Virol 73, 6769-6781 (1999)) rapidly translocate into and out of cellular membranes. In fact, distinct peptide regions have been identified within both of these proteins that are capable of translocating into cellular compartments either alone or in combination with chereric cargo peptides, and proteins (Lindgren, M., et al., Trends Pharmacol Sci. 3, 99-103 (2000), Derossi, D., et al, Trends Cell Biol., 8, 84-87 (1998), Prochiantz A., Current Opinion in Cell Biology 12, 400-406 (2000), Steven R. Schwartze, S. R., et al., Trends in Cell Biology 10, 290-295 (2000)). In contrast, full-length Antp protein has not been shown to traverse biological membranes; however, a 16 amino acid synthetic peptide derived from within its coding region does possess potent membrane penetrating abilities (Derossi, D., et al, Trends Cell Biol., 8, 84-87 (1998)). The accepted view of atypical transport used by these molecules has been termed "transduction" (Schwartze, S. R., et al., Trends in Cell Biology 10, 290-295 (2000)), and is currently defined as an extremely rapid membrane transport pathway that is receptor and energy independent, ~~and can occur at 4 C. in all cell types~~ and can occur at 4 ºC in all cell types (Schwartze, S. R.

and Dowdy, S. F. Trends Pharmacol. Sci. 21, 45-48 (2000)). Interestingly, these three proteins are all nuclear proteins involved in transcriptional regulation, and their respective transducing peptides consist of strings of amino acids rich in arginine and lysine (Lindgren, M., et al., Trends Pharmacol Sci. 3, 99-103 (2000), Schwartze, S. R. and Dowdy, S. F. Trends Pharmacol. Sci. 21, 45-48 (2000)). However, irrespective of these similarities, these transducing peptides possess many different characteristics such as amino acid sequence, length of the sequence, cellular localization, and potency of membrane penetration. Thus, though each transducing sequence can penetrate cells and tissues, it has not been established whether they use the identical atypical transport mechanisms.